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REVIEW ARTICLE

The Potential Role of Hypoxia-Inducible Factor-1 in the Progression and Therapy of Central Nervous System Diseases

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Abstract: Hypoxia-inducible factor-1 (HIF-1) is a heterodimer protein composed of an oxygen-regulated functional subunit, HIF-1α, and a structural subunit, HIF-1β, belonging to the basic helix-loop-helix family. Strict regulation of HIF-1 protein stability and subsequent transcriptional activity involves various molecular interactions and is primarily controlled by post-transcriptional modifications. Hypoxia, owing to impaired cerebral blood flow, has been implicated in a range of central nervous system (CNS) diseases by exerting a deleterious effect on brain function. As a master oxygen-sensitive transcription regulator, HIF-1 is responsible for upregulating a wide spectrum of target genes involved in glucose metabolism, angiogenesis, and erythropoiesis to generate the adaptive response to avoid, or at least minimize, hypoxic brain injury. However, prolonged, severe oxygen deprivation may directly contribute to the role-conversion of HIF-1, namely, from neuroprotection to the promotion of cell death. Currently, an increasing number of studies support the fact HIF-1 is involved in a variety of CNS-related diseases, such as intracranial atherosclerosis, stroke, and neurodegenerative diseases. This review article chiefly focuses on the effect of HIF-1 on the pathogenesis and mechanism of progression of numerous CNS-related disorders by mediating the expression of various downstream genes and extensive biological functional events and presents robust evidence that HIF-1 may represent a potential therapeutic target for CNS-related diseases.

Keywords: Hypoxia-inducible factor-1, central nervous system, neuroprotection, apoptosis, angiogenesis, erythropoiesis, inflammation.

1. INTRODUCTION

Oxygen is an essential substance for the stability of the internal environment and the metabolism of tissues and cells. Tissue oxygenation is mainly based on a steady-state of oxygen consumption through mitochondrial oxidative phosphorylation and oxygen delivery to tissues by erythrocytes traveling along capillary beds to achieve a dynamic balance of oxygen supply and demand in the body [1]. However, once any function of mammalian cells in maintaining oxygen homeostasis is disturbed and damaged, it may lead to hypoxia and inevitable oxidative stress, especially in tissues and cells that are highly sensitive to oxygen deficiency, for example, the central nervous system (CNS) [2, 3]. Importantly, both hypoxia and hyperoxia bring harm to the body. Hypoxia results in insufficient ATP to maintain basic cellular functions and plays a crucial role in the pathophysiology and induction of many fatal diseases [1, 4]. In contrast, hyperoxia results in the production of reactive oxygen intermediates with profound cytotoxicity and causes potentially fatal damage to cell membranes and DNA [1, 5].

As a nuclear transcription factor, hypoxia-inducible factor-1 (HIF-1) is critical for mediating oxygen homeostasis in the human microenvironment [2, 4, 6]. Its expression and activity are tightly regulated by cellular oxygen concentrations, mainly through the up-regulation of various physiologically important genes which participate in biological processes, such as neovascularisation, erythrogenesis, cell survival or proliferation, and glucose metabolism and transportation, in addition to energy metabolism, to enable tissues and cells to adapt rapidly to low oxygen concentrations [6, 7]. However, the genes induced by HIF-1 exert different roles across different diseases [4], for example, HIF-1 can induce the transcriptional activation of oncogenic growth factors such as epidermal growth factor, transforming growth factor β3 (TGF-β3), and promote tumor metastasis to oxy-

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gen-rich distant tissues [8]. Furthermore, in ischemic cardiovascular disease, HIF-1 likely has a protective role in the compensatory hypertrophic stage of heart failure by stimulating adaptive angiogenesis [9]. Ackeret *et al.* emphasized that the role of HIF-1 in the CNS is more complex and highly dependent on the cellular background [10]. Recently, an increasing number of studies have been devoted to exploring the close relationship between HIF-1 and the CNS. Therefore, this review mainly focuses on the structure and biological function of HIF-1, its association with related diseases in the CNS, and its potential as a therapeutic target.

2. STRUCTURAL AND REGULATION ANALYSIS OF HIF-1

2.1. The Structural Characteristics of HIF-1

HIF-1, a core transcription factor involved in the regulation of oxygen homeostasis, exists widely in mammalian and human cells. It was first proposed in 1992 by Semenza and colleagues in the study of erythropoietin (EPO) gene expression [11]. A cis-regulatory DNA with the core nucleotide sequence 5′-RCGTG-3′ was found in the 3-flanking region of the EPO gene, induced by the kidney and liver in hypoxic conditions. These specific DNA fragments, as an enhancer or promoter, can significantly upregulate the transcriptional activity of the EPO gene in response to hypoxia. The fragments were identified as the hypoxia response element (HRE), and the specific protein factor that binds to the HRE site and has transcriptional activation ability was defined as HIF-1 [11, 12]. Subsequently, numerous studies analyzed the structure of HIF-1 through the purification of HIF-1 by DNA affinity chromatography and the coding sequence of its cDNA [7, 13-15].

HIF-1 is a heterodimer composed primarily of an HIF1-α subunit with a molecular weight of 120kD complexed with a 91-94kD HIF1-β subunit, which is also known as an aryl hydrocarbon receptor nuclear translocator (ARNT) [13, 15]. The HIF1-β subunit is the protein product of the ARNT gene and is constitutively expressed in the nucleus independent of oxygen, which was originally found as a binding partner of the aryl hydrocarbon receptor (AHR) [16, 17]. The HIF-1α subunit is an 826 amino acid protein. Its gene was mapped to human chromosome 14q21-q24 and it is highly regulated by cellular oxygen concentration [7, 13, 15]. HIF-1 belongs to the basic helix-loop-helix–Per-ARNT-Sim (bHLH–PAS) transcription factor family [7, 13]. The primary structure of both the HIF-1α and HIF-1β subunits share the following common domains [7, 18]: (1) the bHLH at its N-terminus is the hallmark of a broad superfamily of transcription factors and an essential structure for mediating protein dimerization and DNA binding [18, 19]; and (2) a required structural dimerization motif, the PAS, was initially described by the presence of related sequences in the PER, ARNT, and SIM proteins, which constitute the mammalian dioxin receptor. All PAS domains contain two internal homologous units of approximately 50 amino acids, specific A and B fragment repeats, and are involved in protein-protein interactions [7, 18, 20]. In fact, the bHLH–PAS structural motifs are essential to mediate HIF-1α and HIF-1β dimerization and facilitate binding to the HRE-DNA sequence to stimulate the transcription of their target genes [8, 17, 21]. Additionally, the amino acids 531–826 of HIF-1α contain two transactivation domains (TAD), namely, N-terminal (N-TAD, amino acids 531–575) and C-terminal (C-TAD, amino acids 786–826). TADs can interact efficiently with co-activators, such as CREB binding protein (CBP) and p300, which fulfill both structural and catalytic roles in the process of stimulating transcriptional activation [5, 22]. Notably, HIF-1α subunits differ from HIF1-β subunits in that they also carry an oxygen-dependent degradation domain (ODDD), a highly conserved structure that is located in the central region of HIF-1α, overlaps the N-TADs, and is responsible for oxygen-regulated stability *via* the ubiquitin proteasome pathway [22, 23]. As described below, these functional domains play a crucial role in regulating HIF-1 activity under normoxic and hypoxic conditions.

Shortly following the discovery of HIF-1α, several independent groups identified two other isoforms of the HIF-a subunit, namely, HIF-2α and HIF-3α [24, 25]. HIF-2α was first discovered in vascular endothelial cells (also called EPAS), which shares close sequence similarity with HIF-1α (up to 48% of the amino acid sequence). This explains their common structural and biochemical ability to heterodimerize with HIF-1β and bind to HREs [24]. Of note, HIF-1α and HIF-2α are distinctly different in their tissue expression, that is, HIF-2α is more abundantly and selectively expressed in endothelial cells, lung, *etc.* [24, 26], whereas HIF-1α is transiently stabilized and mainly mediates acute responses to oxygen deprivation. In addition, previous studies have demonstrated that the HIF-2α protein is associated with chronic hypoxia [27, 28]. Unlike HIF-1α and HIF-2α, relatively little is known about HIF-3α. The bHLH-PAS domain of this protein contains amino acid sequences that share 57% and 53% identity with HIF-1α and HIF-2α, respectively [25]. Furthermore, a spliced variant of the HIF-3α locus, also known as the inhibitory PAS domain protein (IPAS), functions as a negative regulator of HIF-1 by interacting directly with the HIF-1α subunit and preventing its DNA-binding activity [29]. A schematic representation of HIF subunit structures is represented in Fig. (**1**).

2.2. The Regulation of HIF-1

The activation of HIF transcription factors mainly depends on the stabilization of the redox-sensitive α-subunit [30]. The HIF-1α protein has a short half-life of 5 min and numerous studies have confirmed that this process is easily regulated by oxygen tension [31]. In contrast, HIF-1β, as a constitutively expressed subunit, is synthesized and degraded regardless of oxygen availability [30, 32]. Under normoxia, and despite being synthesized, HIF-1α is susceptible to instantaneous degradation, leading to barely detectable expression of HIF-1α [30, 31]; whereas under hypoxia, HIF-1α increases and then translocates into the nucleus where it heterodimerizes with the β-subunit to form an active transcription factor [30]. The canonical regulation of the specific transcriptional potency and stability of the HIF-1 protein primarily involves a series of molecular interactions and is controlled *via* post-transcriptional modifications [33, 34], as explained in detail below.

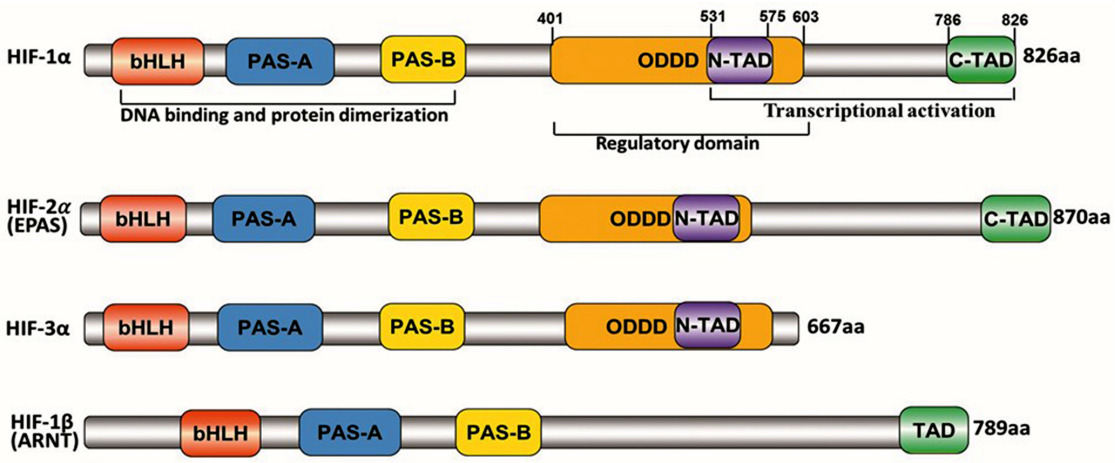

Fig. (1). A schematic diagram of hypoxia-inducible factor (HIF) subunit structures. The family of HIF proteins is depicted by conserved bHLH and PAS domains that are involved in DNA binding and heterodimerization. Additionally, HIF-*α* isoforms also contain an oxygen dependent degradation domain (ODDD) domain that is responsible for oxygen-dependent hydroxylation and degradation. In contrast to HIF-1*α* and HIF-2*α* that contain two transcriptional activation domains (N-TAD, C-TAD), HIF-β only has one TAD. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

2.2.1. The Regulation of HIF-1 Protein Stability

In normal oxygen concentrations, HIF-1α protein expression is negatively regulated by the ubiquitin-proteasome pathway [31]. The prolyl hydroxylase domain (PHD), a member of the 2-oxoglutarate (2-OG)-dependent dioxygenase family, hydroxylates two conserved proline residues, pro-402 and pro-564, located in the ODDD domain of the oxygen-sensitive alpha subunit [35, 36]. Studies have confirmed that PHDs contain three different isozymes in all mammals (PHD-1, PHD-2 and PHD-3), most significantly PHD2 (also referred to as EGLN1), and is known to be the key limiting enzyme that hydroxylates and destabilizes HIF-1α *in vivo* [35, 37]. Furthermore, PHDs are highly dependent on sufficient oxygen and 2-oxoglutarate as co-substrates, in addition to ascorbic acid and Fe^{2+} as cofactors, to carry out hydroxylation [8, 38]. Subsequently, the hydroxylated proline residues are sensitively bound to the E3 ligase complex, including the von-Hippel-Lindau protein (pVHL), serving as a substrate recognition unit, and interacts with Elongin-B, Elongin-C, Cullin-2 (Cul-2), and Ring-Box 1(RBX1), which induces poly-ubiquitinating HIF-1*α* and finally results in its degradation *via* the 26S proteasome [23, 34, 39]. Moreover, Jeong *et al.* concluded that lysine 532 in the ODDD of HIF-1α was acetylated by arrest defective protein (ARD1), causing rapid acceleration of HIF1-α subunit interaction with pVHL and ultimately induced pVHL-mediated ubiquitination. However, ARD1, as a negative regulator of HIF-1α stability, plays a more prominent role in normoxia because the expression of ARD1 mRNA is limited under hypoxia, which directly results in a decreased affinity for HIF-1α [17, 40].

2.2.2. The Regulation of HIF-1 Transcriptional Activity

In addition to protein stabilization by PHDs and pVHL mentioned above, another regulatory mechanism of HIF-1α is through the modulation of transcriptional activity by the hydroxylation of asparagine, phosphorylation, and small ubiquitin-related modifier (SUMO), *etc.*

Factor inhibiting HIF (FIH) is an asparaginyl hydroxylase that recognizes signals of transcriptional inhibition, which can catalyze asparagine residue 803 (Asn803) located within the C-TAD domain in normal oxygen conditions, causing the C-TAD domain of HIF-1α not to combine with the transcriptional co-activators CBP/p300. Like the PHDs, FIH is also a 2-OG-dependent dioxygenase and its activity is required for certain requisite cofactors such as Fe^{2+} and ascorbate [41]. Therefore, during hypoxia, neither PHD nor FIH can cause hydroxylation, which enables stable dimerization of HIF-1α and HIF1-β to form a HIF-1 complex that interacts with HREs, causing various target gene transcription mediating adaptations in response to the hypoxic conditions [6, 11, 42] (Fig. **2**).

Numerous studies have demonstrated that strong activation of mitogen-activated protein kinase (MAPK) elicits direct HIF-1α phosphorylation and enhances HIF-1-mediated transcriptional gene expression activity [43]. Thr796 in HIF-1α and Thr844 in HIF-2α are phosphorylation sites modified by p42/p44 MAPK, which is crucial for up-regulation of the transcriptional response in a low oxygen environment by improving the binding capacity of the CAD domain and transcriptional coactivator CBP [43, 44]. The phosphorylation of Thr-796 prevents the hydroxylation of Asn-803 by FIH and further stabilizes the HIF-1 protein [45]. Interestingly, MAPK also causes phosphorylation of Ser-641/643, which facilitates the efficient nuclear accumulation and transcriptional activity of HIF-1 by inhibiting its CRM1-dependent nuclear export [46].

SUMOylation, a reversible post-translational protein modification, has been widely reported to be accomplished through a multistep enzyme cascade and plays a significant role in complicated protein regulatory processes, including transcriptional regulation, nuclear transport, and signal transduction [47, 48]. Bae *et al.* first reported that the protein level and transcriptional activity of HIF-1a was improved by SUMO-1 modification at two lysine residues (Lys391 and Lys477), and that SUMOylation of lysine residues probably

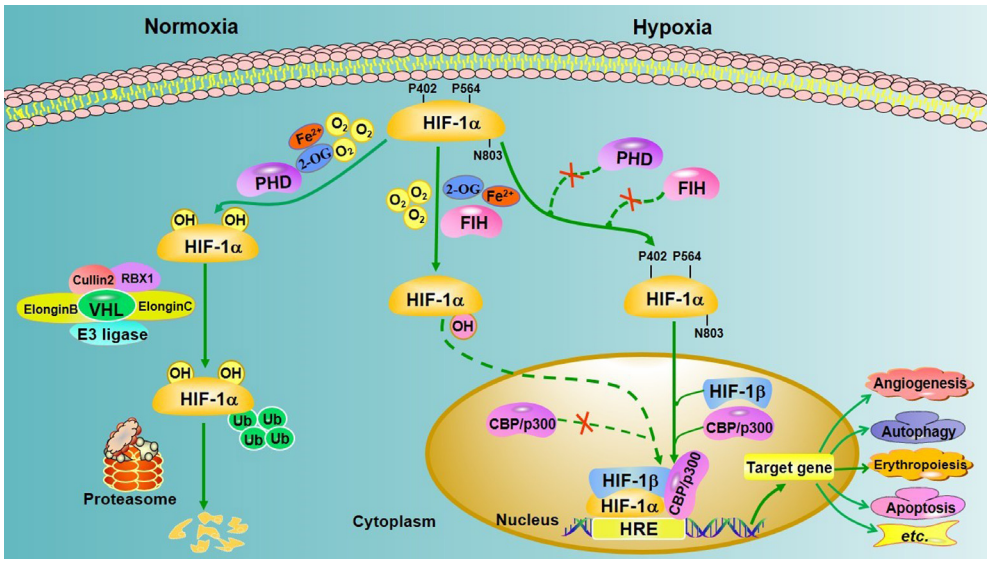

Fig. (2). Illustration of the regulation of hypoxia-inducible factor-1 (HIF-1) stability and transcription under normoxic and hypoxic conditions. During normoxia, the proline residues pro-402 and pro-564 of HIF-1a are hydroxylated by prolyl hydroxylase domains (PHDs) and subsequently bind to von-Hippel-Lindau protein (pVHL)-mediated ubiquitination, resulting in its degradation by the 26S proteasome. In addition, factor inhibiting HIF (FIH) can hydroxylate the asparagine residue Asn-803, which causes HIF-1α not to interact with the transcriptional co-activators CREB binding protein (CBP)/p300. In low oxygen conditions, the hydroxylation of the PHD and FIH is inhibited, and the HIF-1α protein becomes stabilized and subsequently translocates into the nucleus where it heterodimerizes with the β-subunit to form an HIF-1 complex that interacts with hypoxia response elements (HREs) and transcriptional coactivators (p300/CBP), ultimately inducing a sequence of target gene expression. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

inhibits ubiquitin attachment sites and subsequently proteasomal degradation [49]. Conversely, subsequent studies have held the opposite conclusion that SUMO modification of HIF-1α suppresses its transcriptional activity [50]. Interestingly, SUMO conjugation is known to be a dynamic process and easily reversed by the Sentrin/SUMO-specific proteases (SENPs) family. Furthermore, a study by Cheng proposed that SENP1 specifically targeted HIF-1α for de-SUMOylation, is vital for ensuring HIF1α stability in hypoxia, and that SUMOylation acts as a direct signal for proteasomal degradation [51]. In light of the above findings, the effect of HIF-1α SUMOylation remains controversial and further studies are needed to address this issue [34]. Overall, the regulation of HIF-1 is an extremely complex process, and environmental stimuli, cytokines, growth factors, and other signaling pathways are involved in the regulation and different functions of HIF-1.

3. TARGET GENE AND BIOLOGICAL FUNCTIONS OF HIF-1

In the CNS, neuronal and brain function are highly sensitive to ischemic and hypoxic events [3]. In response, to meet the brain's physiological needs in hypoxia and maintain oxygen homeostasis, HIF-1 serves an essential role in these complicated homeostatic processes by inducing an increased expression of a wide range of target genes and participating in numerous biological functional processes, such as erythropoiesis, angiogenesis, glucose metabolism, inflammation, cell survival, and even apoptosis [2, 17, 52].

3.1. HIF-1 and Angiogenesis

Angiogenesis is an innate physiologic response, which involves three distinct processes, namely, (1) new vessel formation by endothelial progenitor cells (EPCs) during embryogenesis (vasculogenesis), (2) the sprouting of new capillary branches from pre-existing blood vessels (angiogenesis), and (3) remodeling of existing arteries to develop new collaterals (arteriogenesis) [53-55]. In elaborate circulatory systems such as the cerebral microvasculature, neovascularization is critical for additional blood flow to deliver sufficient nutrients and oxygen to neural tissues, to allow for rapid adaptation to pathological, physiological or microenvironmental stimuli [53]. Several studies have reported that hypoxia is the principal physiological stimulus of angiogenesis, which is a complex multi-stage process involving vasodilation, endothelial cell (ECs) proliferation, and migration. This is primarily mediated by HIF-1 transcriptional activation of various critical angiogenic growth factors/cytokines and their receptors, including vascular endothelial growth factor (VEGF), stromal-derived factor 1 (SDF-1), platelet-derived growth factor B (PDGF), placental growth factor (PLGF), angiopoietin (Ang-1 and Ang-2), and stem cell factor (SCF) [54], by binding to their cognate receptors VEGFR1 (Flt-1)/VEGFR2 (Flk-1), CXCR4, VEGFR1, PDGFRα/PDGFRβ, TIE2, and C-KIT, respectively [54, 56, 57]. Among these factors, VEGF is the most potent and essential endothelial-specific mitogen, which participates directly in many steps involved in sprouting angiogenesis. Initially, a hypoxic microenvironment and HIF-1 stimulate VEGF and pro-angiogenic factors mentioned above to interact with their receptor-ligand, activating quiescent ECs to initiate the angiogenic cascade [53, 56]. Thereafter, matrix metalloproteinases (MMPs) initiate the activation and migration of ECs by degrading basal membrane glycoproteins and extracellular matrix components. A study by Ben-Yosef found that HIF-1 significantly enhanced EC migration in an MMP-2-

dependent manner [58]. In addition, HIF-1 encodes VEGF and induces the integrin family to co-mediate EC proliferation, migration, and adhesion, thus contributing to the formation of tubule-like structure [53, 59, 60]. Vessel maturation occurs in the final stages of angiogenesis, and primarily involves the recruitment of supporting cells, such as pericytes and smooth muscle cells (SMCs), to promote vessel maturation and stabilization [53, 56]. A recent *in vitro* investigation of rat primary brain microvascular ECs demonstrated that recombinant adenovirus-mediated HIF-1α (Ad-HIF-1α) dramatically increased the expression of VEGF by enhancing HIF-1α levels under hypoxic situations [61]. Furthermore, VEGF, a critical angiogenic protein involved in vessel remodeling after cerebral stroke, can influence dynamic blood flow, which may be an important factor in the recovery of stroke patients [61, 62]. We conclude that HIF-1 activation may be responsible for the precise coordination of almost the entire process of new vessel sprouting, resulting in direct neuroprotective action and the prevention of ischemic neuronal cell death [10].

3.2. HIF-1 and Erythropoiesis

EPO (a glycoprotein) is the main hematopoietic cytokine that stimulates the viability, differentiation, and proliferation of erythroid precursor cells by binding to the specific cell surface EPO receptor (EPO-R) [63]. EPO is one of the sensitivity genes which is the most regulated by ambient oxygen concentrations. As early as 1992, Semenza found that EPO was the first target gene for HIF-1 by mediating transcriptional induction [11]. Human EPO gene expression occurs mainly in the liver of the fetus and the kidney in adults and is inducible by oxygen deficiency or anemia. In the CNS, EPO mRNA was primarily recognized in astrocytes, and EPO-R expression was present in neurons, astrocytes, and microglia [12, 63, 64]. Similarly, during brain anoxia, HIF-1 markedly elevates brain EPO production, which is responsible for increased erythrocyte production. This leads to increased oxygen delivery to reduce the damaging effects of hypoxia and ischemia on neural tissue [6, 17, 65]. Additionally, Marti *et al.* suggested that EPO may also be involved in angiogenesis by reacting to the mitogenesis of brain ECs *via* activation of the VEGF/VEGFR system to improve tissue oxygenation and blood flow in the ischemic border [66, 67]. Several *in vivo* and *in vitro* studies have established that EPO is a powerful inhibitor of hypoxia-induced neuronal apoptosis, and it also has a direct neurotrophic effect by decreasing inflammation and mediating other pleiotropic neuroprotective processes. Its function depends on the paracrine EPO/EPO-R signal transduction mechanism to cause a series of complex cascade reaction events [65, 68, 69]. This EPO/EPO-R system exerts neuroprotective effects greatly through the autophosphorylation and activation of Janus-tyrosine-kinase-2 (JAK2), which leads to further activation of downstream signaling pathways, including the PIK-3/AKT, STAT-5, and MAPK pathways [70-73]. Moreover, Digicaylioglu *et al.* demonstrated that in cultured neurons, upregulation of EPO by HIF-1 could protect cerebral cortical neurons against NMDA- or NO-induced cell apoptosis by triggering cross-talk between JAK2 and nuclear factor-κB (NF-κB) signal transduction pathways. They concluded that the EPO effect may be the basis of the neuroprotection mediated by hypoxic-ischemic preconditioning. Subsequent studies confirmed this statement, which offers new insights for the development of improved treatment of CNS diseases [74-76].

3.3. HIF-1 and Cell Autophagy

As described above, HIF-1 fulfills an important role in mediating multiple target genes for neuroprotection and adaptive mechanisms against hypoxic and ischemia stress; however, persistent and prolonged activation of the HIF-1 pathway may result in transformed neuronal function, from neuronal protection and survival to cell autophagy and apoptosis. This suggests that the HIF-1 system mediates dual functions related to either cellular survival or death [10, 77].

Under normal physiological conditions, autophagy plays a key role in maintaining cellular homeostasis and basic metabolic requirements by removing potentially harmful substances, such as long-lived organelles and abnormal proteins. Nonetheless, abnormally activated autophagy in pathological situations will trigger type II programmed cell death distinct from apoptosis in neurons [78]. Numerous recent studies have shown that autophagy is easily activated in hypoxic-ischemic brain injury, neurodegenerative diseases (NDDs), and other CNS-related diseases, which may be associated with the up-regulation of HIF-1 expression [78-80]. Carloni *et al.* found that autophagy provides a protective effect in the process of neonatal neurodegeneration after hypoxic-ischemic injury [81]. Subsequently, Mazure *et al.* proposed that, under hypoxia (~3-0.1% O_2), HIF-1 is implicated in autophagy to sustain cell survival mechanisms by rapidly mediating the signaling pathway of atypical BH3-only protein Bcl-2/E1B 19 KDa interacting protein 3 (BNIP3/BNIP3L(NIX)) [80]. Moreover, HIF-1-dependent overexpression of BNIP3 and the constitutive expression of Beclin-1 and Atg5 also stimulate selective autophagy in the mitochondria. This is an adaptive response that can prevent excessive production of reactive oxygen species (ROSs) leading to oxidative stress and cell death under hypoxic conditions [82]. Conversely, autophagy induced under severe hypoxia or anoxia (<0.1% oxygen), concomitant to metabolic stress (low glucose and low pH), is often related to cell death, which is mainly mediated by AMP-activated protein kinase-mammalian target of rapamycin (AMPK-mTOR) and the unfolded protein response (UPR) pathways [80]. Xu *et al.* [78] came to a similar conclusion through different rat models of ischemic/hypoxic cerebral injury, namely. that highly activated autophagy induced by severe hypoxia/ischemia and/or reperfusion, ultimately leads to astrocyte and neuronal death. In determining the final morphology of damaged neurons and astrocytes, their experiment found that autophagy has considerable overlap with apoptosis, necroptosis, and necrosis, and that autophagy activation may be involved in cerebral ischemia-triggered apoptosis and necrosis by mutual interaction [78, 83]. Increasingly, research suggests that HIF-1-mediated autophagy plays a dual role in determining the fate of the cell, that is, it promotes cell survival or death, depending on the cell type and the degree of hypoxia/ischemia [78, 80, 83].

3.4. HIF-1 and Cell Apoptosis

Apoptosis, the tightly-regulated active programmed cell death that normally occurs during development and aging, is considered to be a vital homeostatic mechanism to maintain

the number of cells in tissues, in addition to providing a defense mechanism [84]. Several studies have suggested that apoptosis has a series of morphological characteristics and is involved in cell shrinkage, nuclear chromatin concentration, membrane blebbing, phosphatidylserine exposure, and fragmentation of nuclear DNA into cell membrane-bound structures called apoptotic bodies [78, 85]. These apoptotic features are frequently observed in NDDs and cerebral ischemia, especially in the penumbra after ischemic stroke [83-85]. Carmeliet *et al.* performed oxygen and glucose deprivation treatment on wild-type embryonic stem cells (ES, HIF-$1\alpha^{+/+}$) and embryonic stem cells with inactivated HIF-1α genes (ES, HIF-$1\alpha^{-/-}$), and found that the former decreased cell proliferation and increased apoptosis, while the latter did not cause significant changes, and revealed the new role of HIF-1 in mediating cell apoptosis [86]. Furthermore, this is supported by a subsequent investigation of acute hypoxic injury *in vivo*, showing that mice with late-stage loss of HIF-1α in the brain were protected from hypoxia-induced apoptosis and that HIF-1α deficiency may provide a neuroprotective effect [87]. Current evidence shows that cell apoptosis is mainly mediated by intrinsic (mitochondria) and extrinsic (death-receptor) pathways. Studies by Piret *et al.* and Brunelle *et al.* expounded the intricate mechanism by which HIF-1 may promote apoptosis through up-regulation of a variety of pro-apoptotic molecules and proteins [88, 89], for example, HIF-1 induces the expression of BNIP3 and its homolog NIP3-like protein X (NIX), members of the pro-apoptotic Bcl-2 protein family. These pro-apoptotic Bcl-2 family proteins and pro-apoptotic pore-formers (Bax, Bak), act mainly by regulating the permeability of the outer mitochondrial membrane, causing the irreversible release of space proteins in the membrane, for example, cytopigment C (Cyt C) and apoptosis-inducing factor (AIF), which subsequently activates the caspase-9/caspase-3 pathway and initiates apoptosis [90-92]. Brunelle *et al.* found that oxygen deprivation-induced apoptosis is heavily dependent upon the intrinsic mitochondrial pathway [89]. In addition, several studies demonstrated that numerous genes involved in cell cycle regulation, such as the p53 tumor suppressor protein, were also up-regulated in a HIF-1-dependent manner [17, 93]. Chen *et al.* [94] observed that a high level of HIF-1 has a stable effect on the p53 protein under continuous hypoxic stimulation. Its mechanism of action is to suppress MDM2-mediated p53 ubiquitination and prevent MDM2-mediated nuclear transfer of p53, so that p53 can act on target genes such as Bax, Noxa, Puma, and p21 and ultimately contribute to cell apoptosis and cell cycle arrest [94]. In addition, P53-null mice with middle cerebral artery occlusion (MCAO) had less ischemic damage than their wild-type counterparts, strongly suggesting that p53 is implicated in the regulation of apoptosis following neuronal injury [95]. Likewise, according to a study by Kim *et al.*, HIF-1α can bind directly to the HRE in the Noxa promoter region, increase its expression, and activate apoptosis in hypoxia by inducing ROS-dependent cytochrome c and caspases release [96]. Moreover, the c-Jun N-terminal kinases (JNKs, also referred to as stress-activated protein kinases), crucial neuronal signaling effectors, perform an important role in neuronal apoptosis through activation of multiple mechanisms, such as phosphorylating and activating p53 and Bax [92].

3.5. HIF-1 and Inflammation

Inflammation is a defensive response to harmful stimuli and conditions which serves to recruit a variety of inflammatory mediators to the site of injury to eliminate pathogens and harmful substances, thus maintaining normal tissue function and homeostasis [97]. However, unresolved or uncontrolled inflammation forms the basis of a series of disorders, including atherosclerosis [98]. Hypoxia is a prominent feature of chronic inflammatory tissues and their microenvironment. The infiltration and high metabolism of inflammatory cells lead to increased oxygen demand during tissue inflammation, in addition to a deficient blood flow in inflamed tissues that directly decreases oxygen supply [98]. Tissue hypoxia activates the HIF signaling pathway, which is a key transcriptional regulator of immune cell effector function [99]. NF-κB, a major regulatory-related gene involved in innate immunity and inflammation, is strongly activated following the stimulation of cells with specific pro-inflammatory ligands, such as toll-like receptors (TLR), cytokines and antigens; it also shows sensitivity to hypoxia [98, 99]. Recently, substantial cross-talk between the HIF-1 and NF-κB signaling pathways has been demonstrated [100]. Indeed, the NF-κB subunits p50 and p65 can bind directly to a κB binding site at −197/−188bp in the HIF-1α promoter under hypoxic conditions, thereby increasing HIF-1α mRNA levels and protein expression in response to pro-inflammatory mediators tumor necrosis factor-α (TNF-α) or bacterial lipopolysaccharide [98, 100, 101]. Interestingly, Scortegagna *et al.* conducted a mouse keratinocyte experiment and further demonstrated that HIF-1 overexpression is involved in two signaling networks that increase the autonomous activation of NF-κB, mainly including the hyperphosphorylation of IκB and ERK1/2-mediated phosphorylation of Ser-276 on p65, which, respectively, enhance the nuclear localization and transcriptional activity of p65 and subsequently facilitate an intense inflammatory hypersensitivity through the generation of pro-inflammatory cytokines and chemokines, for example, CXCL1, macrophage inflammatory protein (MIP)-2 and TNF-α [102]. These studies suggest that the regulation of the NF-κB and HIF-1 pathways in hypoxic, inflamed tissues is highly interdependent and interconnected. Neutrophils and monocytes/macrophages and dendritic cells (DCs) are the primary innate immunity cells, the activation of these cells can rapidly eradicate pathogens and transmit signals that amplify adaptive immune responses [103, 104]. Furthermore, a growing body of research has highlighted that HIF-1 is essential for regulating immune cell function by medicating glycolysis and energy metabolism, subsequently stimulating the adhesion, aggregation, motility and invasion of myeloid cells [103, 105]. A study by Peyssonnaux *et al.* also found that the loss of HIF-1α may result in a significant attenuation of the bacterial killing power of myeloid cells. In contrast, when the HIF-1 control pathway is activated, it may be involved in the expression of antimicrobial peptides, granule proteases, NO, TNF-α, and other significant immune effector factors, thereby enhancing the bactericidal power of phagocytes and effectively preventing the spread of bacterial infections [106]. HIF-1α also prevents neutrophils from undergoing apoptosis; hypoxia may further stimulate the secretion of MIP-1β to promote neutrophil survival [107]. Moreover, several studies

have claimed that HIF-1α is involved in cell migration, survival, metabolism, and the antigen-presenting function of DCs in hypoxic and inflammatory states, but the role of HIF-1 in inducing cytokines of DCs remains controversial [98, 105, 108, 109]. Of note, a role for HIF-1α has also emerged in adaptive immunity. HIF-1α has been reported to impact the survival, differentiation and function of different T cell subsets under both normoxic and hypoxic conditions, such as cytotoxic T-cell (CD8+), T helper (Th) and T regulatory (T-Reg) cells [98, 105]. For example, HIF-1α can favor CD4+ Th17 cells development by transcriptionally activating RORγt expression to further promote interleukin (IL)-17 production, thereby regulating Th17 cell signature genes; additionally, HIF-1α-driven glycolytic shift also facilitates Th17 cell differentiation [110]. More recently, in a systematic review by McGettrick *et al.*, authors found that HIF dysregulation is closely linked to various immune-mediated disorders [105]. In summary, these findings support the view that HIF-1 plays a pivotal role in the pathway that regulates immune cell function in the context of different microenvironments.

4. THE ROLE OF HIF-1 IN CNS-RELATED DISEASES

A large body of evidence indicates that HIF pathways may regulate an array of downstream target genes in order to adapt to hypoxia and maintain oxygen homeostasis in the brain. Recently, several studies have emphasized the significant role of HIF-1 in the pathology of numerous CNS-related diseases. Therefore, it may be a potential therapeutic target for neurological disorders.

4.1. Atherosclerosis (AS)

Intracranial and extracranial atherosclerosis is recognized worldwide as the main cause of ischemic stroke and transient ischemic attack and is associated with a high risk of stroke recurrence. Large-artery atherosclerosis is primarily caused by arterio-arterial embolism, hypoperfusion, branch atherosclerotic disease (occlusion of small perforating arteries), and other mechanisms that lead to ischemic stroke [111]. AS is a very common chronic inflammatory disease. Endothelial dysfunction is a key factor driving the development of AS, and low-density lipoprotein (LDL) accumulates and infiltrates into the subendothelial space. Concurrently, ECs secrete various growth factors that enable monocytes to aggregate and adhere to the intima. Monocytes can be converted into macrophages with scavenger effects, and continuously take up oxidized LDL (ox-LDL) to form foam cells. Likewise, activated SMCs undergo migration and proliferation and can also phagocytize lipid to form muscle-derived foam cells, and are ultimately implicated in the formation of fibrous caps. Additionally, persistent inflammation characterizes AS, and also gives rise to complications, such as thrombosis and plaque rupture, which may lead to ischemic events caused by large artery stenosis [112, 113]. Chronic hypoxia is one of the main causes of the progression of atherosclerosis, and HIF plays a pivotal role in the pathogenesis of AS [114]. ECs can maintain vascular homeostasis through various mechanisms such as recruiting different inflammatory mediators, regulating the blood flow tension gradient, and providing a barrier function. However, once ECs are exposed to hypoxia, these mechanisms are disturbed [115]. In a mouse model experiment, Akhtar *et al.* observed high HIF-1α expression in EC nuclei of atherosclerotic lesions. Compared with EC-HIF-1$\alpha^{+/+}$ mice, the area of carotid artery lesions in mice with knocking out the HIF-1 gene in EC (EC-HIF1$\alpha^{-/-}$) was obviously reduced. And mildly ox-LDL (and its derivative lysophosphatidic acid) can increase the expression of HIF-1α in ECs, thereby inducing miR-19a-mediated CXCL1 expression and monocyte recruitment and ultimately contribute to the progression of AS [116]. Subsequently, Feng *et al.* investigated the potential mechanisms of HIF-1α in focal EC dysfunction and inflammation associated with early AS. HIF-1α can be activated by mechanical shearing of arterial ECs, leading to its preferential expression in atheroprone sites. The expression of HIF-1α is mediated by the dual mechanisms of transcriptional activation by NF-κB and stabilization by the deubiquitinating enzyme Cezanne. This leads to the accumulation of HIF-1 in low shear regions that drives AS by facilitating excessive proliferation and inflammation of ECs by upregulating glycolysis enzymes. Furthermore, a study by Feng first reported that the noncanonical mechanical activation of HIF-1 is a novel mechanism in the initiation of focal AS, suggesting that this pathway may provide opportunity for new therapeutic targets for the prevention and treatment of early AS [117]. Moreover, several studies have found that HIF-1α can induce various inflammatory cells to participate in the pathophysiology of AS, and of these inflammatory cells, macrophages are the main inflammatory mediators, exerting its action by directly promoting plaque formation and influencing AS disease progression by modulating cholesterol homeostasis [112, 114]. Additionally, macrophage migration inhibitory factors (MIF), an important mediator of vascular remodeling in AS, can be overexpressed *via* HIF-1α-dependent pathways to mediate the migration and proliferation of vascular smooth muscle cells (VSMCs), leading to narrowing of the large arteries [118]. In the late stage of atherosclerosis, plaque neovascularization is an adaptive consequence of long-term hypoxia [112]. HIF-1 is strongly linked to angiogenesis by stimulating multiple angiogenesis target genes such as VEGF, MMP-2, PIGF, *etc.* [54, 58]. Furthermore, according to a study by Higashida *et al.* that investigated carotid artery atherosclerosis in humans, HIF-1α also participates in the deep layer of plaque angiogenesis by expressing E26 transformation specificity-1 (Ets-1), which may exacerbate the risk of vulnerable plaque hemorrhage and ulceration [119]. A recent study demonstrated that contrast-enhanced ultrasound (CEUS) is a non-invasive and readily available imaging method that can be used to evaluate the characterization of carotid atherosclerotic plaques, such as intraplaque neovascularization and ulceration, which may guide early prophylactic treatment and effectively prevent the occurrence of clinically adverse events such as TIA and ischemic stroke [120]. Furthermore, HIF-1α is implicated in apoptosis, which in late AS may promote the instability of the fibrous cap, and increase the risk of rupture and thrombus formation [114, 121]. Taken together, these studies show that HIF-1 exerts a key role in mediating the complex development of AS. A recent review highlighted that HIF-1 might serve as a potential treatment target for AS. Moreover, Rahtu-Korpela *et al.* suggested that HIF-prolyl 4-hydroxylase (HIF-P4H-2, also referred to as PHD2) inhibition by FG-4497 may be a novel therapeutic approach to

prevent the progression of AS by reducing cholesterol levels and inflammation and regulating the innate immunity [122].

4.2. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a common NDD characterized by progressive dementia. The main pathological features of AD are the formation of extracellular senile plaques due to the overproduction of beta-amyloid (Aβ) and the aggregation of hyperphosphorylated tau protein into neurofibrillary tangles [123]. Additionally, hypometabolism and activation of astrocytes in specific regions of the brain are also vital components of the pathological characteristics of AD [124, 125]. Aβ peptide accumulation promotes the production of ROS. The increased levels of ROS and cytokines cause oxidative stress and the activation of inflammatory mechanisms, which facilitates neuronal damage and cognitive decline [123]. HIF-1 has been shown to have a neuroprotective role in AD, primarily through the inhibition of the neurotoxicity induced by ROS and Aβ protein [124, 126]. Soucek *et al.* suggested that the activation of HIF-1 may be involved in protecting nerve cells against Aβ peptide toxicity by generating sufficient reduction equivalents through glycolysis and the hexose monophosphate shunt (HMS) pathway [127]. Interestingly, low levels of Aβ can up-regulate HIF-1 expression, which is conducive to promoting the glucose metabolic pathway to yield more antioxidants (for example,. NADH and NADPH) to reduce Aβ-induced oxidative stress [10, 127]. Schubert *et al.* investigated how the induction of HIF-1 may prevent astrocyte activation by Aβ, and explored in detail the therapeutic value of the metal chelator desferoxamine (DFO), which promotes the stability of HIF-1α by inhibiting PHD and proteasomes in the AD model. DFO is also involved in combating free radicals yielded by iron and delaying the progression of AD [125, 128]. Furthermore, an *in vivo* and *in vitro* study found that HIF-1 can suppress $A\beta_{25\text{-}35}$ peptide-induced hippocampal neuronal apoptosis and that recombinant adeno-associated virus vector expressing the human HIF-1α gene (rAAV-HIF-1α) is an effective gene therapy for AD [129]. HIF-1 has been shown to be an effective neuroprotective agent in the treatment of NDDs, especially AD [126]. M30, a novel multifunctional iron chelator that is able to cross the blood brain barrier (BBB), can modulate the HIF-1α signaling pathway activity, and thereby elevate the levels of HIF-1α mRNA and protein expression. This promotes the expression of a wide range of neuroprotective HIF-1α-related target genes, such as EPO, VEGF, glucose transporters (GLUT), and P21. The pharmacological multimodal effect of M30 not only markedly attenuated the generation of phosphorylated tau protein by inducing the glycogen synthase kinase-3β signaling pathway, but also protected cortical neurons from Aβ25-35 neurotoxicity [128]. Furthermore, evidence shows that EPO improves neurological outcomes of experimental AD by alleviating tau hyperphosphorylation, oxidative stress, neuronal loss, *etc.*, while the expression of Epo/EpoR and its cytoprotective function is heavily controlled by HIF-1 [130]. Neuro-EPO, a new EPO formulation with the advantage of being able to cross the BBB, has been shown to have neuro-protective effects in different biological models of NDDs. In a recent animal study, it was found that APPSwe mice, an AD transgenic mouse model, efficiently mitigated its recognition memory, apoptosis, neuro-inflammation, and Aβ load after intranasal administration of Neuro-EPO, suggesting the Neuro-EPO may be a potent therapeutic strategy for AD [131].

However, severe or prolonged hypoxia can transform HIF-1 into an activator of molecular processes that are detrimental to cells, causing the formation and accumulation of Aβ peptides, dysregulation of Ca^{2+} homeostasis, aggravation of neuro-inflammation, and even neuronal apoptosis. Iyalomhe *et al.* suggested that this is more likely to occur in the late stage of AD [123, 124]. The findings of a study by Zhang *et al.* reported that in hypoxia, HIF-1 increased the overexpression and enzyme activity of β-site amyloid precursor protein cleaving enzyme (BACE1), thereby contributing to increased generation of β-amyloid precursor protein (APP) and Aβ protein. Furthermore, their findings suggested that there was an increased incidence of AD and vascular dementia following cerebral ischemia and stroke [132]. Additionally, Aβ and hypoxia can induce microglial activation. Microglia are important immune cells and are involved in neuroinflammation that causes the release of pro-inflammatory chemokines/cytokines (for example, IL-1 and IL-6) and ROS-generation. The increased inflammatory mediators and ROS heavily exacerbate the pathology of AD [133]. In addition, an investigation of primary cortical neurons in rats detected that Aβ induced oxidative stress in a HIF-1-dependent manner to activate pre-apoptotic factor BNIP3 expression, which contributes substantially to neuronal death [134]. It is worth noting that the accumulation of Aβ and hypoxia jointly cause disruption of Ca^{2+} homeostasis, and intracellular Ca^{2+} excess and ROS accumulation also trigger the cascade of apoptosis induced by mitochondrial dysfunction [124, 133]. An increasing number of studies investigating HIF-1 in AD have illustrated its significance as an essential regulatory factor of neuroprotective or detrimental effects in different contexts, which suggests that further detailed studies investigating the role of HIF-1 as a potential therapeutic target for the treatment of NDDs are required [123, 124].

4.3. Ischemic Stroke

Stroke is an acute cerebrovascular disease with sudden onset and rapid brain function impairment. According to the 2016 global disease burden study, stroke has become a leading cause of disability and death in the world, of which ischemic stroke (IS) accounts for 80% of cases [135]. Ischemic stroke refers to a clinical syndrome in which blood supply to the brain is impaired due to a variety of reasons, leading to ischemia, hypoxic necrosis of brain tissue, and the resultant neurological deficits. Several recent studies have reported that HIF-1α serves as a pivotal transcription factor that regulates oxygen levels and plays a key role in the pathology and outcome of ischemic stroke. It is of concern that HIF-1 may induce dual cascade reactions (namely, beneficial or harmful) in cerebral ischemia, which may largely depend on the duration and severity of the hypoxic-ischemic injury [6, 77]. On the one hand, Baranova *et al.* showed that transient MCAO-induced focal cerebral ischemia directly triggers the marked increase of HIF-1α protein expression. Furthermore, the neuron-specific conditional knockdown of HIF-1α in mice after MCAO can intensify the brain injury and decrease survival rate. Conversely, in the wild model, after being treated with pharmacological activators to enhance its activi-

ty, HIF-1 greatly attenuated the severity of ischemic damage [136]. Moreover, HIF-1α can accumulate and trigger VEGF, EPO, GLUT-1 and GLUT-3, glycolytic enzymes, and inducible nitric oxide synthase (iNOS) genes to initiate neuroprotective mechanisms in response to cerebral hypoxia and ischemia [6]. A recent study demonstrated that the ischemic penumbra of a rat stroke model treated with Ad-HIF-1α attenuated active caspase-3 and apoptosis in neurons by upregulating EPO expression. Furthermore, the study suggested that the ischemic penumbra is still the major focus of ischemic stroke therapy and that efficiently salvaging any surviving neurons appeared to be conducive to the recovery of neural function [68]. Moreover, HIF-1-dependent EPO also has a neurotrophic effect, suppresses the inflammatory response, and contributes to neuro-angiogenesis in ischemic injury. Several studies have reported that the nasal application of Neuro-EPO is an effective inducer of endogenous neuroprotection and that Neuro-EPO may be a reliable therapeutic option for ischemic stroke [67, 69, 137]. Preconditioning refers to the fact that moderate hypoxic or ischemic events elevates the tolerance of tissues and organs, which may protect tissues from the lethal stress and injury caused by subsequent long-term hypoxia or ischemia. An increasing number of studies have shown that hypoxic preconditioning is primarily mediated by the activity of HIF-1, which usually involves the protective mechanism of multi-factor adaptability described above (such as GLUT-1, EPO, and iNOS genes). This protective effect has been well established in the brain [10]. A study investigated the potential protective mechanism of distal limb (remote) ischemic preconditioning (RIPC) to prevent brain damage caused by stroke. This was achieved by inducing the HIF-1α-mediated increase of the anti-inflammatory factors IL-4 and IL-10 in the peripheral blood which reduced the infarction area and facilitated functional neural recovery [138]. In addition, it was reported that RIPC-mediated protection from cerebral ischemia/ reperfusion (I/R) injury also involves the HIF-1α/ AMPK/ HSP70 pathway [139] and the administration of both DFO and $CoCl_2$, two vital inducers of HIF-1, may offer a protective effect similar to that of hypoxic preconditioning to resist hypoxic-ischemic damage [77]. Increasingly, researchers are investigating possible inhibitors of PHDs that may offer neuroprotection against transient and permanent focal cerebral ischemia by increasing HIF-1α protein levels, which provides new insight into the possible therapeutic role of HIF-1α in ischemic stroke [6, 140, 141]. However, HIF-1α has been shown to cause the expression of various pro-apoptotic genes, including BNIP3, Bax, NIX, *etc.*, and subsequently the activation of mitochondria-mediated caspase-dependent neuronal apoptosis in cerebral ischemia. Furthermore, the high expression of HIF-1α is closely related to the stabilization of the p53 protein that assists in coordinating the expression of apoptosis-related proteins, which results in hypoxia-mediated delayed neuronal death [6, 77, 92]. According to a study conducted by Cheng *et al.*, the overexpression HIF-1α may assist with Notch-1 signaling to exacerbate inflammation and neuronal apoptosis in focal ischemic stroke [142]. Recent research explored the potential molecular mechanisms and the role of HIF-1α in the neuroinflammatory response during I/R. The study provides further evidence that the NLRP3 inflammasome, the key mediator of post-ischemic inflammation, may be activated by HIF-1α to intensify apoptotic and pyroptotic cell death following stroke. In addition, the inhibition of HIF-1α by YC-1 markedly suppresses the expression of NLRP3/caspase-1. The reduction of CD68 immune cells and MPO immune cell infiltration also relieves neuroinflammation, thereby decreasing the infarction volume and cell death after ischemic stroke. This suggests that attenuating neuroinflammation with HIF-1α inhibition may be a potential method to reduce apoptosis after stroke, which warrants further research [143].

4.4. Subarachnoid Hemorrhage (SAH)

Cerebral ischemia induced by cerebral vasospasm (CVS) after SAH is closely related to early brain injury (EBI). EBI is considered to be the main cause of death and morbidity after SAH, which usually involves neuronal cell death, BBB disruption, increased intracranial pressure, decreased cerebral blood flow, brain oedema, and other pathophysiological changes [144]. Ostrowski *et al.* demonstrated for the first time that high expression of HIF-1α was observed in the acute cerebral ischemic area 24 hours after experimental SAH in rats. HIF-1α immunoreactive expression was the greatest in pyramidal neurons of the hippocampal CA1 region, and colocalization with TUNEL-positive cells occurred mainly in the nuclei of neurons. In addition, HIF-1α protein expression accompanied by upregulation of BNIP3 and VEGF may be involved in promoting apoptosis and destruction of the BBB, respectively, and it is speculated that hyperbaric oxygen therapy may alleviate EBI after SAH by inhibiting HIF-1α and its target genes [145]. The results of a subsequent study also showed that the inhibition of HIF-1α by 2-methoxyestradiol (2-ME2) significantly improved EBI in SAH by downgrading downstream targets [144]. Additionally, a further study has clearly elucidated the potential relationship between HIF-1α, aquaporin-4 (AQP-4), and MMP-9 protein in the pathophysiological cascade reaction that leads to brain oedema. HIF-1α also serves a pivotal role in exacerbating BBB dysfunction and brain oedema formation through molecular signaling pathways involving these proteins. Nevertheless, inhibiting HIF-1α through 2-ME2 intervention could reverse the adverse outcome of EBI, which offers novel insights into effective pharmacologically targeted treatment for SAH patients [146]. Yan *et al.* showed that the stable expression of HIF-1α protein in the basilar artery (BA) is a significant factor in promoting the development of CVS after SAH, and that 2-ME2 markedly reduced CVS by inhibiting VEGF expression and attenuating BNIP3-induced endothelial and VSMCs apoptosis and proliferation [147]. Conversely, a study that investigated the rat double-hemorrhage model of SAH found differently, namely, that induced DFO can enhance HIF-1α protein activity, and that overexpression exerted evident attenuation of BA vasospasm and decreased brainstem blood flow [148]. Additionally, a very recent study reported that argon therapy might reduce mortality following experimental SAH and ameliorate functional outcomes, possibly dependent on the potential mechanism of upregulated HIF-1α-induced continuous heme oxygenase expression [149]. Taken together, these findings suggest that the role of HIF-1α in SAH, whether beneficial or deleterious, remains undetermined and its potential therapeutic neuroprotective value requires further investigation.

Table 1. Summary of potential functions of HIF-1 in different CNS-related diseases.

Related Diseases	Models or Cells Studied	Effects of Active HIF-1 Expression	Involved Main Molecules or Signaling Pathways	References
Atherosclerosis (AS)	Mouse endothelial cells (Ecs)	Promotes inflammation.	Endothelial HIF-1α/miR-19a pathway upregulates CXCL1 expression and monocyte adhesion; Activates the NF-κB inflammatory pathway and enhances HIF-1 expression via the positive feedback loop.	[116]
	Porcine and murine arteries	Induces excessive EC proliferation and inflammation.	HIF expression depends on NF-κB and Cezanne; HIF-1α promotes glycolysis gene in low shear stress.	[117]
	Human umbilical artery smooth muscle cells (HUASMCs)	Stimulates the expression MIF mediating VSMCs proliferation and migration.	Generates intercellular ROS and activates ERK signaling pathway.	[118]
	Human carotid plaques	Induces angiogenesis.	Upregulates HIF-1a/VEGF/Ets-1 cascade.	[119]
Alzheimer's Disease (AD)	Mouse astrocytes	Reduces astrocyte activation.	DFO stabilizes HIF-1 to enhance glycolysis and HMS pathways.	[125]
	Cultured PC12 and B12 cells	Protects cells against Aβ protein neurotoxicity.	Enhances glucose metabolism and the HMS to generate sufficient reducing equivalents.	[127]
	Cultured cortical neurons	Decreases phosphorylated tau; Protects cells from Aβ25-35 neurotoxicity.	Upregulates multiple HIF-1-dependent target genes (VEGF, EPO, glycolytic enzymes, and p21).	[128]
	Primary cultured hippocampal neurons	Inhibits hippocampal neuronal apoptosis.	rAAV-HIF-1α inhibits intracellular up-regulation of Ca^{2+}.	[129]
	Mouse neuroblastoma N2a cells	Increases Aβ production.	Enhances BACE1 expression and enzyme activity, leading to increase the APP/Aβ.	[132]
	Rat primary cortical neurons	Induces neuronal death.	Mitochondrial oxidative stress mediates Aβ neurotoxicity; The pro-apoptotic gene BNIP3 expression in an Aβ/ROS/HIF-1-dependent manner.	[134]
Ischemic Stroke	Rat transient MCAO stroke model and neurons and astrocytes	Inhibits neuronal apoptosis and improves neurological functional recovery.	Ad-HIF-1α up-regulates EPO expression and inhibits the activation of caspase-3 in neurons.	[66]
	CCAO rat stroke model and neural cells	Increases neuronal apoptosis.	Upregulates pro-apoptotic genes.	[85]
	Mouse transient focal cerebral ischemia model and brain tissues	Reduces brain injury.	Mediates the neuronal survival genes (EPO, VEGF, Flt-1, Flk-1, PAI-1, GLUT-1, enolase, and Ang-2) and proapoptotic factors (bNIP-3, Noxa, RTP801and Nix).	[136]
	Rat MCAO and RIPC model; Peripheral blood and ischemic penumbra tissue	Improves anti-inflammatory protein levels and decreases infarct size.	Elevates levels of anti-inflammatory cytokines in peripheral blood (IL-4 and IL-10).	[138]
	PC12 cells and primary rat neurons	Decreases neuronal apoptosis; induces autophagy.	Protects cells against oxygen-glucose deprivation insult.	[140]
	Focal cerebral I/R mice model and cultured cortical neuron	Increases neuronal apoptosis; Exacerbates inflammation.	Increased levels of NF-κBp65 / p-p65.	[142]
	Focal cerebral ischemia model and rat brain tissues	Promotes pyroptotic and neuronal apoptosis; Enhances neuroinflammation.	Regulates HIF/ NLRP3 / caspase-1 pathway; Increases the expression of IL-1β and IL-18.	[143]

(Table 1) contd….

Related Diseases	Models or Cells Studied	Effects of Active HIF-1 Expression	Involved Main Molecules or Signaling Pathways	References
Subarachnoid Hemorrhage (SAH)	Rat brain and basilar artery	Enhances cerebral vasospasm.	Elevated the expression of BNIP3, VEGF, and PCNA protein.	[144]
	SAH rat model and brain tissue	Increases neuronal apoptosis and BBB disruption.	Up-regulates the expression of VEGF and BNIP3 protein.	[145]
	SAH rat model and brain tissue	Increases brain oedema and BBB destruction.	Induces AQP-4/ MMP-9 signaling pathway.	[146]
	Rat basilar artery and brainstem	Attenuates cerebral vasospasm and reduces brainstem blood flow.	Induces the HIF-1/VEGF pathway.	[148]
	SAH rat model and brain tissue	Reduces neuronal mortality after SAH.	Upregulates HIF-1α-induced consecutive HO-1 expression.	[149]

CONCLUSION

Here, we have provided a summarized overview of the significant role of post-translational modification in the regulation of HIF-1α activity and stability. HIF-1 is an extremely crucial transcription factor responsible for maintaining oxygen homeostasis and it induces adaptive survival mechanisms to cope with the adverse physiological and pathological conditions caused by hypoxia. Based on the large body of current evidence, HIF-1 is responsible for upregulating the expression of numerous genes and mediating signal transduction pathways, thereby inducing the protective responses against neurodegenerative disorders and cerebrovascular disease. Therefore, HIF-1α may be a potential novel therapeutic target for the treatment of CNS-related diseases.

However, several *in vivo* and *in vitro* studies have found that HIF-1 not only mediates the adaptive mechanisms that cause neuroprotective effects but also leads to cell death phenomena, which may primarily be related to the duration and severity of hypoxia and ischemia and the phosphorylation status of the HIF-α subunits. Hence, finding an effective approach to balance the beneficial versus potentially detrimental effects and other cellular events of HIF-augmenting therapy requires further research. Moreover, specific cell types, the selective cellular target and microenvironment, and crosstalk between other potential signaling molecules and HIF-1 are all significant aspects that need to be considered. Further research on these aspects may improve our understanding of the role of HIF-1 in cerebral ischemic disease and other pathological CNS-related conditions. Although evidence supports the notion that specific PHD inhibitors and Neuro-EPO act as neuroprotective agents in preventing neuronal damage, further research is required to translate these potential strategies into human clinical trials and confirm their precise therapeutic effects.

In summary, HIF-1 plays a prominent role in the complicated molecular processes involved in the progression of CNS disorders. Further research on novel specific PHD inhibition, or HIF-1 as a key target, may provide great potential for therapeutic intervention of neurological diseases in the future.

LIST OF ABBREVIATIONS

PAS = Per-ARNT-Sim

EPAS = Endothelial PAS protein

ERK = Extracellular Signal-Regulated Kinase

VEGFR = Vascular Endothelial Growth Factor Receptor

Flt-1 = Fms-Related Tyrosine Kinase-1

Flk-1 = Fetal Liver Kinase-1

CXCR4 = C-X-C Chemokine Receptor Type 4

VSMCs = Vascular Smooth Muscle Cells

PIK3/AKT = Phosphatidylinositol-3-Kinase/Serine-Threonine Kinase

STAT-5 = Signal Transducer and Activator of Transcription-5

NMDA = N-methyl-D-aspartate

NO = Nitric Oxide

NADH = Nicotinamide Adenine Dinucleotide

NADHP = Nicotinamide Adenine Dinucleotide Phosphate

CCAO = Common Carotid Artery Occlusion

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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